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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/092,243	03/06/2002	Jeffrey Daniel Hillman	00-505-I	9604

20306 7590 03/16/2005

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EXAMINER	
SHIBUYA, MARK LANCE	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 03/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/092,243	HILLMAN, JEFFREY DANIEL	
	Examiner	Art Unit	
	Mark L. Shibuya	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *13-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/4/02 and 8/25/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-22 are pending. Claims 13-22 are withdrawn from consideration. Claims 1-12 are examined.

Election/Restrictions

2. Applicant's election of Group I, claims 1-12, in the reply filed on 7/23/2004 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Claims 13-22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the replies filed on 7/23/2004 and 12/6/2004.

Priority

4. The instant application states that it is a continuation in part of Serial No. 09/980,845, filed 11/15/2001; which is the national stage of PCT/US00/21340, international filing date; which claims benefit of U.S. Provisional Application 60/147,551, filed 8/6/1999.

5. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

This application is claiming the benefit of a prior filed nonprovisional application under 35 U.S.C. 120, 121, or 365(c). At least one common named inventor between the current application and the prior application is required. See, 35 U.S.C. § 120.

Upon inspection of the inventorship as entered in the PALM computer system, it appears that the inventive entity of the prior filed nonprovisional application, 09/980,845, *i.e.*, sole inventor Ann Progulske-Fox, does not share at least one common named inventor with the inventive entity of the instant application, *i.e.*, sole inventor Jeffrey Daniel Hillman. The examiner has ordered the original file wrapper of application no. 09/980,845, but has not yet received application no. 09/980,845 for inspection of inventorship. If applicant believes, in fact, that the instant application and application no. 09/980,845, share a common named inventor, the applicant should state on the record.

6. The elected invention of Group I, drawn to methods of identifying a polynucleotide expressed *in vivo*, comprising *probing a phage display library* with absorbed antibodies, does not find descriptive or enabling support in PCT/US00/21340 or 60/147,551. Therefore, the elected invention of Group I is accorded priority only to the filing date of the instant application, filed 3/6/2002.

Oath/Declaration

7. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

In the Declaration entered 5/20/2002, applicant has listed PCT US00/21340 as a prior foreign application, but instead should claim benefit of PCT US00/21340 under 35 U.S.C. 120.

Information Disclosure Statement

8. The IDS entered 6/4/2002 has been fully considered and initialed, but reference no. 22, to Handfield et al., has been crossed out because it is duplicative of reference no. 16. The IDS entered 8/25/2003 has been fully considered but reference no. 2, to Suk et al, has been crossed out because it is duplicative of reference no. 21 of the IDS entered 6/4/2002.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-7 and 9-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for pooled antisera from diseased human, does not reasonably provide enablement for antibody not produced from infected animals or humans. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to method of identifying a polynucleotide of a microbe that is expressed *in vivo*, comprising the steps of: (a) adsorbing antibodies against antigens that are expressed by the microbe *in vivo* and *in vitro* with cells or cellular extracts of the microbe that have been grown *in vitro*; (b) isolating unadsorbed antibodies; and probing a display library of the microbe's DNA or RNA with the unadsorbed antibodies of step (b); wherein the step of probing a display library comprises: (i) immobilizing the

unadsorbed antibodies on a solid support; (ii) adding the display library of the microbe's DNA or RNA to the solid support; (iii) washing unbound phage from the solid support and (iv) recovering phage that are bound to the solid support; wherein a polynucleotide of the microbe that is expressed *in vivo* is isolated and identified.

There are many factors be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether undue experiment is necessitated. These factors can include, but are not limited to:

(1) the breadth of the claims;
(2) the nature of the invention;
(3) the state of the prior art;
(4) the relative skill of those in the art;
(5) the level of predictability in the art;
(6) the amount of direction provided by the inventor;
(7) the existence of working examples; and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(1 and 2) The breadth of the claims and the nature of the invention: The claims recite methods of identifying polynucleotides that encode a microbial antigen found only *in vivo* by adsorbing out antibodies that bind *in vitro* microbial antigens. No other limitations are placed upon the antibodies, and as such, this could read on a wide variety of origins of such antibodies. The instant specification at p. 27, line 1-p. 29, line 8, states that "[p]olypeptides or polynucleotides of the invention can be used to elicit an immune response in a host." The instant specification states:

> A polypeptide or a polynucleotide of the invention can be administered to an animal, such as a mouse, rabbit, guinea pig, macaque, baboon,

> chimpanzee, human, cow, sheep, pig, horse, dog, cat, chicken, and duck, to elicit antibodies *in vivo*. Injection of a polynucleotide has the practical advantages of simplicity of construction and modification.

Specification at p. 27, lines 19-22. The specification contemplates antibodies produced by injecting polypeptides or polynucleotides into human and animals, including chickens and ducks. Thus the claims are very broad in scope of encompassed subject matter, particularly in regard to the origins and quantities of the antibodies used.

(3 and 5) The state of the prior art and the level of predictability in the art

Methods for making for producing antibodies that bind microbial *in vivo* antigens, were known at the time of filing; however, the art only teaches the production of antibodies that do not bind antigens found on cultured microbes, from the sera of infected humans or animals. For example, the review article of Rollins et al., Cellular Microbiology (2005) Vol. 7, No. 1, pp. 1-9, at p. 2, para 2-p. 3, para 2, teaches using serum from patients infected with a pathogen of interest. Given the use of cultured microbes to adsorb antibodies that bind antigens found *in vitro*, as disclosed in the instant application, one of skill in the art would not be able to predict that antibodies not produced from sera of infected humans or animals would have antibodies that specifically bind antigens not expressed *in vitro*.

(4) The level of one or ordinary skill: The level of skill would be high, most likely at the Ph.D. level. However, such persons of ordinary skill in this art, *given its unpredictability*, would have to engage in undue (non-routine) experimentation to carry out the invention as claimed.

(6-7) The amount of direction provided by the inventor and the existence of working examples: The Specification at p. 12, line 20-p. 13, line 5, states that the sample of antibodies are from the serum of "a host or hosts currently infected with or previously infected with the microbe" and states that "[b]ecause a host from which serum is collected has undergone or is actively engaged in an actual infection by the microbe of interest, the host's serum contains antibodies produced against microbial antigens expressed during the in vivo infectious process." All examples use antibodies originally from infected human patients.

(8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure: The claims contain only broad recitations of antibodies. However, the instant specification does not provide to one skilled in the art a reasonable amount of guidance with respect to the direction in which the experimentation should proceed in carrying out the full scope of the claimed methods. Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496 and n.23, 20 USPQ2d 1438, 1455 and n.23 (Fed. Cir. 1991). Therefore, it is deemed that further research of an unpredictable nature would be necessary to make or use the invention as claimed. Thus, due to the inadequacies of the instant disclosure, undue experimentation would be required of one of ordinary skill in the art to practice the full scope of the claimed invention.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, (and dependent claims), recites "unadsorbed antibodies" in lines 6, 7-8, and 9, which renders the claim vague and indefinite because the antibodies of step (a) may be said to be "unadsorbed", having not yet been adsorbed with microbes; "unadsorbed" may also mean the non-subtracted antibodies. Thus the term is capable of more than one meaning. Claim 1, (and dependent claims), recites the limitations "phage" in lines 12 and 13. There is insufficient antecedent basis for this limitation in the claim.

Claim 4, (and dependent claims), recites the limitation "an antigen". There is uncertain antecedent basis for this limitation in the claim. The relationship of the antigen in claim 4 to the "antigens" in claim 1, line 3, is unclear.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Progulske-Fox, WO 01/11081; Granoff et al., US 6,048,527; and Bargatze et al., US 2004/0247611. The instant application is accorded priority only to its filing date of 3/6/2002. *See*, above section entitled *Priority*.

The claims are drawn to method of identifying a polynucleotide of a microbe that is expressed *in vivo* comprising the steps of: (a) adsorbing antibodies against antigens that are expressed by the microbe *in vivo* and *in vitro* with cells or cellular extracts of the microbe that have been grown *in vitro*; (b) isolating unadsorbed antibodies; and probing a display library of the microbe's DNA or RNA with the unadsorbed antibodies of step (b); wherein the step of probing a display library comprises: (i) immobilizing the unadsorbed antibodies on a solid support; (ii) adding the display library of the microbe's DNA or RNA to the solid support; (iii) washing unbound phage from the solid support and (iv) recovering phage that are bound to the solid support; wherein a polynucleotide of the microbe that is expressed in vivo is isolated and identified.

Progulske-Fox et al., WO 01/11081, throughout the publication, at p. 3, lines 10-16, teach *in vivo* induced antigen technology (IVIAT) methods for identifying polynucleotides expressed by a microbe during infection of a host, comprising adsorbing antibodies against antigens that are expressed by the microbe *in vivo* and *in vitro* with cells or cellular extracts of the microbe that have been grown *in vitro*; and isolating unadsorbed antibodies with microbes grown *in vitro*. In the Examples, at p. 27,

line 20, Progulske-Fox et al. teach pooling antisera from human patients suffering periodontal disease and absorbing the antisera with whole cells and cell extracts of *Actinobacillus actinomycetemcomitans*, (*Aa*), immobilized on nitrocellulose. Progulske-Fox et al., at p. 29, Example 2, teach making a genomic expression library containing *Aa* DNA in an inducible expression system that was then transformed into *E. coli*. The *E. coli* were replica plated out onto nitrocellulose membranes; the membranes were blocked and probed with adsorbed serum. Reactive *E. coli* colonies were recovered. In Example 3, p. 32, the cloned inserts were sequenced to characterize polynucleotides of *Aa* that encode *in vivo* antigens.

Progulske-Fox et al. do not teach methods using phage display libraries, and wherein the antibodies, which remain after adsorption with microbes, are immobilized onto a solid support, the phage display library is added to the solid support, the unbound phage is washed from the support and the phage still bound to the support is recovered.

Granoff et al., US 6,048,527, at col. 9, lines 20-35, teach producing polyclonal sera that does not cross-react with host tissue by in-situ absorption. Granoff et al. at col. 15, line 13-col. 16, line 2, teach purifying phage display libraries by biotinylating antibodies, incubating the phage with biotinylated antibody and immobilizing the phage on streptavidin-coated plates, purifying the phage by affinity purification, cloning and sequencing the DNA of the phage. Ganoff et al., at col. 23, line 51-63, col. 27, lines 1-16, teach the use of blocking buffer in antibody methods in order to reduce non-specific binding of the antibodies (as in instant claim 2).

Bargatze et al., US 2004/0247611, throughout the publication and at para [0150] teach methods for identifying polynucleotides that encode microbial antigens and affinity purification of phage bearing epitopes comprising mixing phage with sepharose beads (reading on supports) conjugated to monoclonal antibodies, incubating, loading the bead-bound phage into columns; affinity purifying the phage, and eluting the bound phage from the column.

It would have been prima facie obvious at the time the invention was made for one of ordinary skill in the art to have used methods of identifying a polynucleotide of a microbe comprising absorbing antibodies with microbes, wherein the antibodies, which remain after adsorption with microbes, are immobilized onto a solid support, the phage display library is added to the solid support, the unbound phage is washed from the support and the phage still bound to the support are recovered.

One of ordinary skill in the art would have been motivated to have immobilized onto a solid support, the antibodies remaining after adsorption, and to have added the phage display library to the solid support, washing the unbound phage from the support and recovering the phage still bound to the support, because Ganoff teaches the specific antibody selection of polynucleotides encoding antigens borne on phage display libraries, and Bargatze teaches conjugating antibodies to a solid support in order to immobilize appropriately expressing phage from phage display libraries; and because both Ganoff and Bargatze teach antibody affinity purification of phage displaying the appropriate antigen, which eliminates the steps of replica plating, identifying appropriate replica clones by antibody and then selecting the corresponding original clones on the

original culture plates, as in the methods taught by Progulske-Fox. One of ordinary skill in the art would have had a reasonable expectation of success in using the specific post-adsorption antibodies to probe phage display libraries, because Ganoff and Bargatze teach using specific antibodies to probe such libraries; and Bargatze also teaches conjugating antibodies to solid supports for use in probing such libraries.

12. Claims 1-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Handfield et al., Trends In Microbiology, (July 2000), Vol. 8, No. 7, pp. 336-339; Granoff et al., US 6,048,527; and Bargatze et al., US 2004/0247611. The instant application is accorded priority only to its filing date of 3/6/2002. *See*, above section entitled *Priority*.

The claims are drawn to method of identifying a polynucleotide of a microbe that is expressed *in vivo* comprising the steps of: (a) adsorbing antibodies against antigens that are expressed by the microbe *in vivo* and *in vitro* with cells or cellular extracts of the microbe that have been grown *in vitro*; (b) isolating unadsorbed antibodies; and probing a display library of the microbe's DNA or RNA with the unadsorbed antibodies of step (b); wherein the step of probing a display library comprises: (i) immobilizing the unadsorbed antibodies on a solid support; (ii) adding the display library of the microbe's DNA or RNA to the solid support; (iii) washing unbound phage from the solid support and (iv) recovering phage that are bound to the solid support; wherein a polynucleotide of the microbe that is expressed in vivo is isolated and identified.

Handfield et al., throughout the publication, and abstract, teach *in vivo* induced antigen technology (IVIAT) methods for identifying polynucleotides expressed by a

microbe during infection of a host, comprising adsorbing antibodies against antigens that are expressed by the microbe *in vivo* and *in vitro* with cells or cellular extracts of the microbe that have been grown *in vitro*; and isolating unadsorbed antibodies with microbes grown *in vitro*. At p. 336, para 3-4, Handfield et al. teach pooling antisera from human patients suffering periodontal disease and absorbing the antisera with whole cells and cell extracts of *Actinobacillus actinomycetemcomitans*, (*Aa*), immobilized on nitrocellulose. Handfield et al., at p. 337, Figures 1 and p. 338, Figure 2, teach making a genomic expression library containing *Aa* DNA in an inducible expression system that was then transformed into *E. coli*. The *E. coli* were replica plated out onto nitrocellulose membranes; the membranes were blocked and probed with adsorbed serum. Reactive *E. coli* colonies were recovered. The cloned inserts are then sequenced to characterize polynucleotides of *Aa* that encode *in vivo* antigens.

Handfield et al. do not teach methods using phage display libraries, and wherein the antibodies, which remain after adsorption with microbes, are immobilized onto a solid support, the phage display library is added to the solid support, the unbound phage is washed from the support and the phage still bound to the support is recovered.

Granoff et al., US 6,048,527, at col. 9, lines 20-35, teach producing polyclonal sera that does not cross-react with host tissue by in-situ absorption. Granoff et al. at col. 15, line 13-col. 16, line 2, teach purifying phage display libraries by biotinylating antibodies, incubating the phage with biotinylated antibody and immobilizing the phage on streptavidin-coated plates, purifying the phage by affinity purification, cloning and sequencing the DNA of the phage. Ganoff et al., at col. 23, line 51-63, col. 27, lines 1-

16, teach the use of blocking buffer in antibody methods in order to reduce non-specific binding of the antibodies (as in instant claim 2).

Bargatze et al., US 2004/0247611, throughout the publication and at para [0150] teach methods for identifying polynucleotides that encode microbial antigens and affinity purification of phage bearing epitopes comprising mixing phage with sepharose beads (reading on supports) conjugated to monoclonal antibodies, incubating, loading the bead-bound phage into columns; affinity purifying the phage, and eluting the bound phage from the column.

It would have been prima facie obvious at the time the invention was made for one of ordinary skill in the art to have used methods of identifying a polynucleotide of a microbe comprising absorbing antibodies with microbes, wherein the antibodies, which remain after adsorption with microbes, are immobilized onto a solid support, the phage display library is added to the solid support, the unbound phage is washed from the support and the phage still bound to the support are recovered.

One of ordinary skill in the art would have been motivated to have immobilized onto a solid support, the antibodies remaining after adsorption, and to have added the phage display library to the solid support, washing the unbound phage from the support and recovering the phage still bound to the support, because Ganoff teaches the specific antibody selection of polynucleotides encoding antigens borne on phage display libraries, and Bargatze teaches conjugating antibodies to a solid support in order to immobilize appropriately expressing phage from phage display libraries; and because both Ganoff and Bargatze teach antibody affinity purification of phage displaying the

appropriate antigen, which eliminates the steps of replica plating, identifying appropriate replica clones by antibody and then selecting the corresponding original clones on the original culture plates, as in the methods taught by Handfield. One of ordinary skill in the art would have had a reasonable expectation of success in using the specific post-adsorption antibodies to probe phage display libraries, because Ganoff and Bargatze teach using specific antibodies to probe such libraries; and Bargatze also teaches conjugating antibodies to solid supports for use in probing such libraries.

13. Claims 1-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hautefort et al., Phil. Trans. R. Soc. Lond. B, (2000) Vol. 355, pp. 601-611 (IDS entered 6/6/2002, reference No. 20), Granoff et al., US 6,048,527 and Bargatze et al., US 2004/0247611. The instant application is accorded priority only to its filing date of 3/6/2002. *See*, above section entitled *Priority*.

The claims are drawn to method of identifying a polynucleotide of a microbe that is expressed *in vivo* comprising the steps of: (a) adsorbing antibodies against antigens that are expressed by the microbe *in vivo* and *in vitro* with cells or cellular extracts of the microbe that have been grown *in vitro*; (b) isolating unadsorbed antibodies; and probing a display library of the microbe's DNA or RNA with the unadsorbed antibodies of step (b); wherein the step of probing a display library comprises: (i) immobilizing the unadsorbed antibodies on a solid support; (ii) adding the display library of the microbe's DNA or RNA to the solid support; (iii) washing unbound phage from the solid support

and (iv) recovering phage that are bound to the solid support; wherein a polynucleotide of the microbe that is expressed in vivo is isolated and identified.

Hautefort et al., throughout the publication, and especially at p. 607, para 4, teach *in vivo* induced antigen technology (IVIAT) methods for identifying polynucleotides expressed by a microbe during infection of a host, comprising adsorbing antibodies against antigens that are expressed by the microbe *in vivo* and *in vitro* with cells or cellular extracts of the microbe that have been grown *in vitro*; and isolating unadsorbed antibodies with microbes grown *in vitro*. Hautefort et al. teach pooling antisera from human patients suffering periodontal disease and absorbing the antisera with whole cells and cell extracts of *Actinobacillus actinomycetemcomitans*, (*Aa*). Hautefort et al. p. 29, Example 2, teach making a genomic expression library containing *Aa* DNA in an inducible expression system that was then transformed into *E. coli*.

Hautefort et al. do not teach methods using phage display libraries, and wherein the antibodies, which remain after adsorption with microbes, are immobilized onto a solid support, the phage display library is added to the solid support, the unbound phage is washed from the support and the phage still bound to the support is recovered. Hautefort do not teach blocking non-specific antibodies, and do not teach sequencing the polynucleotides encoding *in vivo* protein.

Granoff et al., US 6,048,527, at col. 9, lines 20-35, teach producing polyclonal sera that does not cross-react with host tissue by in-situ absorption. Granoff et al. at col. 15, line 13-col. 16, line 2, teach purifying phage display libraries by biotinylating antibodies, incubating the phage with biotinylated antibody and immobilizing the phage

on streptavidin-coated plates, purifying the phage by affinity purification, cloning and sequencing the DNA of the phage. Ganoff et al., at col. 23, line 51-63, col. 27, lines 1-16, teach the use of blocking buffer in antibody methods in order to reduce non-specific binding of the antibodies (as in instant claim 2).

Bargatze et al., US 2004/0247611, throughout the publication and at para [0150] teach methods for identifying polynucleotides that encode microbial antigens and affinity purification of phage bearing epitopes comprising mixing phage with sepharose beads (reading on supports) conjugated to monoclonal antibodies, incubating, loading the bead-bound phage into columns; affinity purifying the phage, and eluting the bound phage from the column.

It would have been prima facie obvious at the time the invention was made for one of ordinary skill in the art to have used methods of identifying a polynucleotide of a microbe comprising absorbing antibodies with microbes, wherein the antibodies, which remain after adsorption with microbes, are immobilized onto a solid support, the phage display library is added to the solid support, the unbound phage is washed from the support and the phage still bound to the support are recovered.

One of ordinary skill in the art would have been motivated to have immobilized onto a solid support, the antibodies remaining after adsorption, and to have added the phage display library to the solid support, washing the unbound phage from the support and recovering the phage still bound to the support, because Ganoff teaches the specific antibody selection of polynucleotides encoding antigens borne on phage display libraries, and Bargatze teaches conjugating antibodies to a solid support in order to

immobilize appropriately expressing phage from phage display libraries; and because both Ganoff and Bargatze teach antibody affinity purification of phage displaying the appropriate antigen, which eliminates the steps of replica plating, identifying appropriate replica clones by antibody and then selecting the corresponding original clones on the original culture plates, as in the methods taught by Hautefort. One of ordinary skill in the art would have had a reasonable expectation of success in using the specific post-adsorption antibodies to probe phage display libraries, because Ganoff and Bargatze teach using specific antibodies to probe such libraries; and Bargatze also teaches conjugating antibodies to solid supports for use in probing such libraries.

Conclusion

14. Claims 1-12 are rejected.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Shibuya whose telephone number is (571) 272-0806. The examiner can normally be reached on M-F, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Mark L. Shibuya
Examiner
Art Unit 1639

ms

[illegible]
PRIMARY EXAMINER